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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,855	07/03/2003	Si-Hyoung Lee	DE-1490	4750

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ANDERSON, KILL & OLICK, P.C.
1251 AVENUE OF THE AMERICAS
NEW YORK,, NY 10020-1182

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,855	LEE ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *10-26 and 33-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Newly submitted claims 33-50 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims e.g., claim 33 are drawn to the non-elected inventions. Claims 41 42 and 50, for example, are drawn to a new, distinct and different method from the original method already examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33-50 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

As a preliminary matter, applicants state that there are 50 claims filed on July 3, 2003. A review of the file on the record revealed that there were only 26 claims filed on 7/3/2003. However, there was a statement made that there were 50 claims that were filed. The appendix contained only 26 claims. Additionally, applicants should have called the examiner's attention regarding the missing claims when the Restriction requirement was made on 6/15/2005.

Status of Claims

Claims 1-50 are pending

Claims 10-26 and 33-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-9 and 27-32 are under examination.

Withdrawn Objection and Rejection

The objection to the Drawings has been obviated with the submission of the replacement sheet. The 35 USC 103 rejection over Hayes in view of Short has been withdrawn in view of the amendments to the claims and applicants' arguments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-9 and 27-32, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

Claim 1 drawn to "preparing a library of mutant polynucleotides, each mutant polynucleotide being prepared by a process" is not supported in the as-filed specification. MPEP 704.12 recites that applicants specifically point out where support in the specification can be found. The original disclosure describes preparing a library of mutant polynucleotides comprising the recited steps 1-5 and not that each mutant is prepared by the process steps 1-5.

Written Description Rejection

Claims 1-9, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons reiterated below.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional

characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure indicates that the applicants have invented species sufficient to constitute the gen[us]. Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

The specification provides a written description of the specific enzyme, chitosanase gene as the target gene modified by three specific nucleotides at the defined position of the gene to produce a mutant library of the chitosanase gene. Other than this specific enzyme, no other target gene has been described. Neither do any other transposon and its derivatives or multiple three nucleotides randomly substituted at any target site other than does specifically described has also been completely disclosed. The specification does not show any structural correlation of the single enzyme species, chitosonase, to other enzymes, let alone, to the other huge scope of the structurally

unrelated genus target. None of the components in the method has any defined structure. The numerous factors or variables included in the genus are infinite even for a specific component of the claim. Examples of these factors are the structures of any target DNA that can be mutated by multiple substitution of three nucleotides, the position along the structures where substitution can be done, the length of target DNA i.e., whether the whole or fragment of the DNA is used. The target DNA is only one of the undefined variables of the genus claim. There are still the other undefined variables that also have to be determined and analyzed. For example, the multiple three substituents do not recite the kind of nucleotides that are comprised therein, the type of randomization of the multiple three substituents. Also, the type of transposons, especially its derivatives, which can be inserted and the insertion site and cutting enzymes such that the target DNA would at least retain its function. These are only but a few of the infinite variables covered by the huge scope of the genus claims. In biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be unforeseeable results obtained from species other than those specifically described. The more unpredictable the art the greater the showing required (e.g. by (representative examples)

for both enablement and adequate disclosure. A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials. University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Applicants, at the time of filing, are deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). Applicants are further referred to the CAFC decision in the University of California vs. Eli Lilly and Co. CAFC 43 USPQ2d 1398 7/22/1997 with respect to adequate disclosure of the scope of the presently claimed method. Adequate disclosure, like enablement, requires representative examples, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had

possession of the full scope of the claimed invention. See In re Riat (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University of California v. Eli Lilly and Co. (for disclosure).

Response to Arguments

Applicants argue that it is known to those skilled in the art that random mutagenesis techniques can be universally applied to any target DNA irrespective of its specific nucleotide sequence, length, encoded proteins or desired property. A declaration under 37 CFR 1.132 executed by Si-Hyoung Lee, is argued to demonstrate that the inventive method is also applicable to another DNA i.e., DNA encoding phytase.

In response, it is not controverted that the specification and 132 declaration demonstrate the applicability of the method to the specific enzymes. What is at issue is whether these two specific enzymes correlate or are predictive of the huge scope of the claimed library of mutant polynucleotide that express structurally and functionally different proteins. That is polynucleotide expressing the different proteins such as antibodies/antigens, binding proteins, hormones and others.

Claims 1-9, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons as reiterated below.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the target DNA, transposon, multiple three nucleotide substituents, the randomization of these nucleotides. See further the numerous undefined variables of the genus claim, as defined above.

2). The specification failed to provide working examples for any of the numerous and different types of DNA target, transposon, random nucleotides, the multiples of three random

substituents and screening techniques that can be used in the instant method.

3). The breadth of the claims encompasses a large diversity of mutant DNA target by the random peptide, the predetermination of the sites of variations in a target or the nucleotides involve in the variation. It is well known in the art, that it is often difficult to know where insertions in the gene and its encoded protein for mutations can be done without deleteriously affecting the protein function or its global structure. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods.

4). The state of the prior art is such that techniques are specifically applied for a predetermined protein or target.

5). The art is inherently unpredictable because it is not possible to predict which predetermined (variations) of amino acids would result in the desired random mutant with a desired pharmacologic activity. It is generally known that the conformational freedom that promotes binding, e.g., by modifying

the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds).

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous undefined random peptide in a protein would result in a mutations having a desired property without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such.

Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Applicants have not responded to this rejection hence, it is believed that applicants are acquiescing therewith.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claim 1 is unclear as to how a library is prepared from each mutant polynucleotide. [It appears that a library is formed from the steps rather than each library as a mutant polynucleotide, as the amended claim]. The preamble of **preparing** a library is inconsistent with the last step in the body of the claim involving **screening.**

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 and 27-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Short et al (US 20050124010).

Short discloses at paragraph [1617] a method of generating a set of mutagenized organisms that include the step of cloning. The step of cloning may comprise using a Tn7 transposon-based system. It uses TnsABC Transposase to insert a transposon randomly into the DNA target. Such a system or modifications thereof that take advantage of transposon insertion sequences can be utilized to aid in the cloning of high molecular weight DNA. Such cloning approaches may also be provided for by this invention as a step in cell screening. Short discloses at paragraph [2374] that a library of strains with oriT at random

sites and orientations can be produced by insertion mutagenesis using a transposon which bears oriT. The use of a transposon bearing an oriT provides a quick method of generating such a library. Short discloses at paragraph [2392] libraries of random Mud-P22 insertions can be readily isolated and induced to create pools of phage particles packaging random chromosomal DNA fragments. These phage particles can be used to infect new cells and transfer the DNA from the host into the recipient in the process of transduction. Alternatively, the packaged chromosomal DNA can be isolated and manipulated further by techniques such as DNA stochastic &/or non-stochastic mutagenesis or any other mutagenesis technique prior to being reintroduced into cells (especially recD cells for linear DNA) by transformation or electroporation, where they integrate into the chromosome. Either the intact transducing phage particles or isolated DNA can be subjected to a variety of mutagens prior to reintroduction into cells to enhance the mutation rate. Paragraph [2394] describes the integration of such locked-in P22 prophages at various sites in the chromosome allows flanking regions to be amplified and packaged into phage particles. The Mud-P22 mobile genetic element contains an excision-defective P22 prophage flanked by the ends of phage/transposon Mu. The entire Mud-P22 element can transpose to virtually any location in the chromosome or other episome (eg.

F', BAC clone) when the Mu A and B proteins are provided in trans. Paragraph [2395] describes the locked in prophage are used as generalized transducing phage to transfer random fragments of a donor chromosome into a recipient. The Mud-P22 element acts as a transposon when Mu A and B transposase proteins are provided in trans and integrate copies of itself at random locations in the chromosome. In this way, a library of random chromosomal Mud-P22 insertions can be generated in a suitable host. When the Mud-P22 prophages in this library are induced, random fragments of chromosomal DNA will be packaged into phage particles. When these phages infect recipient cells, the chromosomal DNA is injected and can recombine into the chromosome of the recipient. These recipient cells are screened for a desired property and cells showing improvement are then propagated. At paragraph [2397] it is disclosed that individual insertions near a gene of interest can be isolated from a random insertion library by a variety of methods. At paragraph [2404] it is disclosed that a variety of transposon mediated delivery systems can be employed to deliver genes of interest, either individual genes, genomic libraries, or a library of stochastic &/or non-stochastic mutagenized gene(s) randomly throughout the genome of a host. The transposon delivery vehicle is introduced

into a cell population, which is then selected for recombinant cells that have incorporated the transposon into the genome.

The selection (paragraph [2406]) is typically by any of a variety of drug resistant markers also carried within the transposon. The selected subpopulation is screened for cells having improved expression of the gene(s) of interest. Once cells harboring the genes of interest in the optimal location are isolated, the genes are amplified from within the genome using PCR, stochastic &/or non-stochastic mutagenized, and cloned back into a similar transposon delivery vehicle which contains a different selection marker within the transposon and lacks the transposon integrase gene. In [2407] it is disclosed that a stochastic &/or non-stochastic mutagenized library is then transformed back into the strain harboring the original transposon, and the cells are selected for the presence of the new resistance marker and the loss of the previous selection marker. Selected cells are enriched for those that have exchanged by homologous recombination the original transposon for the new transposon carrying members of the stochastic &/or non-stochastic mutagenized library. The surviving cells are then screened for further improvements in the expression of the desired phenotype. The genes from the improved cells are then

amplified by the PCR and stochastic &/or non-stochastic mutagenized again. This process is carried out recursively, oscillating each cycle between the different selection markers. Once the gene(s) of interest are optimized to a desired level, the fragment can be amplified and again randomly distributed throughout the genome as described above to identify the optimal location of the improved genes. In [3290] said method is applied to the geenartion of a library of CDR-Varient Single-Chain Antibodies. It describes conservative amino acid substitutions frequently incorporated and up to 5 residue positions may be varied to incorporate non-conservative amino acid substitutions as compared to known naturally-occurring CDR sequences. Such CDR sequences can be used in primary library members (prior to first round screening) and/or can be used to spike in vitro shuffling reactions of selected library member sequences. Construction of such pools of defined and/or degenerate sequences will be readily accomplished by those of ordinary skill in the art. Accordingly, the process steps of Short discloses each and element of the broad claimed method.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
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